Arabian Journal of Chemistry (2014) 7, 839–845

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Carboxyterfenadine antacid interaction monitoring by UV spectrophotometry and RP-HPLC techniques

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Received 18 September 2012; accepted 20 January 2013
Available online 29 January 2013

KEYWORDS
Carboxyterfenadine;
Fexofenadine;
Antacid;
UV–Vis spectrophotometer;
HPLC

Abstract Carboxyterfenadine, a primary metabolite of terfenadine, a second generation antihistaminic compound was introduced in therapy as a successor of terfenadine due to its cardiac arrhythmia. There are number of drug interactions of fexofenadine with erythromycin, ketoconazole and alike reported in the literature. In this paper, fexofenadine antacid interaction has been studied in presence of sodium bicarbonate, megaldrate, calcium carbonate, magnesium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, simethicone (dimethylpolysiloxane) and calcium hydroxide by UV–Vis spectrophotometer and high performance liquid chromatography (HPLC). These *in vitro* fexofenadine–antacid interactions were carried out in simulated gastric and intestinal juices and in buffer of pH 7.4 (simulating blood pH) on BP 2005 dissolution apparatus. The results show non-concordant availability of fexofenadine envisaged due to formation of unstable charge transfer complexes.

1. Introduction

Fexofenadine, (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic acid hydrochloride, a primary oxidative metabolite of terfenadine (Amon et al., 2000) is a second generation antihistamine. It does not cross the blood–brain barrier and therefore does not cause drowsiness. The most common adverse reactions include headache, dizziness, drowsiness, nausea, sleepiness, nervousness, nightmares and frequent coughing (Tanizaki et al., 2012; Haberfeld, 2010; Dinnendahl and Fricke, 2010) and rarely cause hypersensitivity (Lee et al., 2011; Mathias et al., 2012). It is well-tolerated and a promising probe for studies of membrane transporter function (Flynn et al., 2011).

There are number of reported drug interactions of fexofenadine. It forms a solid state complex with β-cyclodextrin (Sapkal et al., 2010). Erythromycin and ketoconazole increase the plasma levels of fexofenadine two- to three-fold without influencing the QT interval. The reason for this effect is not well understood and could be caused by increased absorption or re-

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.arabjc.2013.01.011

duced gastrointestinal or biliary secretion (Klopp, 2010; Kamath et al., 2005). It is not to be taken with fruit juice because fruit juice could decrease absorption of the drug (Kamath et al., 2005; Dresser and Bailey, 2003; Kamath et al., 2004). Grapefruit juice can significantly reduce the plasma concentration of fexofenadine. Antacids containing aluminum or magnesium reduce the absorption of fexofenadine (Walther and Holtermüller, 1983).

Antacids neutralize acids leading to several products resulting in insoluble compounds. The neutralization rates and capacities are also affected in presence of organic acids, peptone polypeptides (Flynn et al., 2011; Sapkal et al., 2010). The rate of absorption of drug can also be increased or decreased due to the interference of antacid by changing the ionization state, solubility or pH factors (Romankiewi, 1976; Maton and Burton, 1999; Arayne and Sultana, 1993). Multivalent cations also interfere with the availability of ciprofloxacin (Arayne et al., 2005). The interactions with H2-receptor antagonist reveal that they are not temperature dependant, but pH dependant and occur more frequently in more acidic or basic medium (Shahnaz et al., 2012a; 2012b).

In present paper the *in vitro* release of fexofenadine in presence of sodium bicarbonate, magaldrate, calcium carbonate, magnesium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, simethicone (dimethylpolysiloxane) and calcium hydroxide has been studied in simulated gastric and intestinal juices and in buffer of pH 7.4 simulating blood pH at 37 °C and the drug availability in each case was monitored by UV–Visible spectrophotometer and high performance liquid chromatography (RP-HPLC).

2. Experimental

2.1. Materials

Fexofenadine was gifted by Aventis Pharma (Pvt.) Limited, Pakistan. Antacids were sodium bicarbonate, megaldrate, calcium carbonate, magnesium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, simethicone and calcium hydroxide and all are of pharmaceutical grade passed through 170 Mesh Screen 0.088 mm.

2.2. Reagents

Methanol, hydrochloric acid, potassium chloride, ammonia solution 33%, deionized water. All the reagents used were of analytical grade or purified in the laboratory according to standard procedures (Arayne et al., 2007). Potassium chloride recrystallized before use in water and methanol. All glasswares were washed with chromic acid followed by deionized water, which was freshly prepared in laboratory and used throughout the work.

2.3. Equipments

The dissolution equipment was fabricated as described earlier (Arayne et al., 2007). The rotation speed of the basket assembly was fixed at 1000 ± 0.5 rpm throughout the experiment. The dissolution assembly was immersed in a water bath at 37 ± 0.1 °C. A double beam UV/visible spectrophotometer (Shimadzu) model UV1601 coupled with a P IV computer loaded with UVPC version 3.9 software was used for analysis of drug samples. The quartz cells of 10 mm path length were used. The HPLC system (Shimadzu, Japan) comprised of LC-10 AT VP pump, Rheodyne manual injector fitted with a 20 µL loop, Purospher STAR RP-18 end capped (5 µm, 25 × 0.46 cm) column and SPD-10 A VP UV–VIS detector (Japan) were utilized. Chromatographic system was integrated via Shimadzu model CBM-102 to P IV computer. Shimadzu CLASS-GC software (version 2) was used for data acquisition and mathematical calculations. Bath sonicator (LC-30 H, Elma, Germany); Analytical balance (PL303 Mettler Toledo, USA), Filtration assembly (Sartorius, Goettingen, Germany), Filter papers 0.45 µm, 13 mm (Sartorius, Hannover, Germany); Sartorius Minisart RC 4 Syringe filters 0.45 µm, Whatman 41 filter paper circles of diameter 125 mm (Whatman, Maidstone, England) were also used.

3. Results and Discussion

3.1. Adsorption studies

Interactions with antacids were carried out in simulated gastric juice, simulated intestinal juice and in buffer of pH 7.4 at 37 °C. Antacids used were sodium bicarbonate, calcium hydroxide, calcium carbonate, magnesium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, magaldrate and simethicone. Analysis was conducted by adding 10 mL (1 mmol) fexofenadine solution to the dissolution medium at zero time and after 15 min before collecting the first sample 2 g of each antacid was added to the dissolution medium separately in every individual set of experiment. Aliquots withdrawn were assayed for fexofenadine contents and graphs were plotted between drug concentration and time which showed drug status during and at the end of the experiments.

3.2. Fexofenadine antacids interaction by UV spectrophotometer

Antacids are drugs taken orally to neutralize hydrochloric acid secreted by the stomach. The temporary rise in the pH of gastric content will reduce the pain of peptic ulcer (Fujishima et al., 2008; Tarnawski et al., 2013), in this age of fast food, overeating, and busy schedules, many people frequently complain of heartburn or indigestion. Meal timings are rarely consistent, so meal planning appears out of the question. Gastroesophageal reflux disease is a common disorder that affects every population (Frost-Rud, 1999).

The *in vitro* availability studies of fexofenadine hydrochloride in presence of antacids were individually carried out in simulated gastric juice, simulated intestinal juice and in buffer of pH 7.4 at 37 °C. Antacids used are sodium bicarbonate, calcium hydroxide, calcium carbonate, magnesium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, magaldrate and simethicone. The reaction was started by adding 10 ml of 1 mMole fexofenadine to the dissolution medium at zero time while after 15 min before collecting the sample, 2 gm of each antacid was added to the dissolution medium separately in each individual set of experiment. The results are mentioned in Tables 1–3. Graph has been plotted for the first order dissolution rate constant of drug concentration versus time in each set of experiment in presence or absence of antacids.

Table 1 Concentration of fexofenadine (%) in the presence of antacids at different time intervals in simulated gastric juice at 37 °C.

S. No.	Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
1	Fexofenadine	0.406	0.211	0.197	0.198	0.187	0.182	0.202	0.185	0.183	0.189	0.187	0.192	0.196
2	FX + Sodium bicarbonate	0.448	0.225	0.304	0.353	0.323	0.401	0.342	0.338	0.277	0.281	0.396	0.28	0.263
3	FX + Calcium hydroxide	0.282	0.284	0.236	0.252	0.238	0.224	0.248	0.236	0.245	0.241	0.23	0.238	0.235
4	FX + Calcium carbonate	0.618	0.54	0.359	0.276	0.40	0.905	0.414	0.319	0.555	0.535	0.223	0.358	0.22
5	FX + Magnesium carbonate	0.494	0.35	0.3	0.246	0.23	0.218	0.225	0.246	0.225	0.22	0.224	0.214	0.229
6	FX + Aluminum hydroxide	0.278	0.367	0.251	0.24	0.183	0.352	0.269	0.229	0.214	0.193	0.197	0.206	0.2
7	FX + Magnesium hydroxide	0.373	0.338	0.306	0.268	0.251	0.24	0.245	0.249	0.258	0.253	0.224	0.214	0.229
8	FX + Magnesium tri silicate	0.221	0.398	0.261	0.256	0.27	0.236	0.23	0.228	0.229	0.223	0.231	0.218	0.213
9	FX + Simethicone	0.363	0.469	0.268	0.228	0.223	0.218	0.221	0.248	0.27	0.255	0.226	0.23	0.208
10	FX + Megaldrate	0.203	0.409	0.373	0.308	0.373	0.351	0.37	0.386	0.382	0.388	0.387	0.383	0.394

Table 2 Concentration of fexofenadine (%) in the presence of antacids at different time intervals in buffer pH 7.4 at 37 °C.

S. No.	Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
1	Fexofenadine	0.167	0.166	0.163	0.164	0.163	0.168	0.168	0.176	0.18	0.174	0.18	0.18	0.198
2	FX + Sodium bicarbonate	0.142	0.504	0.39	0.326	0.338	0.31	0.308	0.295	0.31	0.3	0.29	0.3	0.295
3	FX + Calcium hydroxide	0.198	0.351	0.256	0.227	0.226	0.219	0.223	0.229	0.229	0.244	0.247	0.267	0.251
4	FX + Calcium carbonate	0.165	0.321	0.211	0.203	0.189	0.19	0.198	0.188	0.198	0.194	0.189	0.203	0.205
5	FX + Magnesium carbonate	0.400	0.434	0.339	0.307	0.304	0.303	0.295	0.3	0.298	0.298	0.297	0.31	0.2987
6	FX + Aluminum hydroxide	0.605	0.512	0.406	0.378	0.382	0.377	0.374	0.389	0.363	0.368	0.00	0.362	0.379
7	FX + Magnesium hydroxide	0.201	0.425	0.251	0.265	0.241	0.23	0.219	0.228	0.276	0.252	0.247	0.223	0.256
8	FX + Magnesium tri silicate	0.21	0.433	0.27	0.242	0.239	0.239	0.232	0.231	0.23	0.248	0.248	0.247	0.247
9	FX + Simethicone	0.859	0.388	0.285	0.257	0.228	0.229	0.22	0.228	0.224	0.222	0.216	0.214	0.222
10	FX + Megaldrate	0.231	0.343	0.215	0.197	0.2	0.197	0.214	0.193	0.195	0.198	0.206	0.203	0.192

Table 3 Concentration of fexofenadine (%) in the presence of antacids at different time intervals in stimulated intestinal juice at 37 °C.

S. No.	Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
1	Fexofenadine	0.071	0.106	0.103	0.101	0.107	0.103	0.101	0.099	0.102	0.095	0.098	0.103	0.122
2	FX + Sodium bicarbonate	0.66	0.607	0.724	0.702	0.678	0.644	0.66	0.717	0.622	0.62	0.549	0.73	0.535
3	FX + Calcium hydroxide	0.4	0.871	0.62	0.547	0.522	0.499	0.523	0.503	0.492	0.486	0.478	0.477	0.469
4	FX + Calcium carbonate	1.307	0.638	0.397	0.349	0.324	0.314	0.31	0.306	0.338	0.307	0.388	0.404	0.36
5	FX + Magnesium carbonate	0.072	0.428	0.222	0.437	0.547	0.266	0.21	0.243	0.164	0.151	0.253	0.156	0.154
6	FX + Aluminum hydroxide	0.139	0.591	0.503	0.481	0.469	0.459	0.453	0.436	0.438	0.461	0.422	0.436	0.413
7	FX + Magnesium hydroxide	0.239	0.66	0.367	0.306	0.308	0.293	0.329	0.329	0.353	0.299	0.284	0.318	0.301
8	FX + Magnesium tri silicate	0.404	0.604	0.487	0.5	0.565	0.616	0.678	0.671	0.667	0.667	0.656	0.655	0.659
9	FX + Simethicone	0.251	0.635	0.407	0.326	0.358	0.304	0.293	0.282	0.273	0.256	0.276	0.268	0.27
10	FX + Magaldrate	0.617	0.669	0.484	0.433	0.4	0.388	0.391	0.378	0.378	0.386	0.378	0.393	0.388

The purpose of this study was to elucidate the potential clinical relevance and mechanism of action of antacids on fexofenadine in simulated gastric juice at 37 °C. 10 ml of 1 mmole of fexofenadine is added and after 5 min 2 g sodium bicarbonate is added at 15 min; the availability of fexofenadine is shown in Tables 1–3. The % availability of fexofenadine in simulated gastric juice with sodium bicarbonate, calcium carbonate and magnesium carbonate was greater than fexofenadine (0.406–0.494%) Figs. 1–5. While in presence of calcium hydroxide, aluminum hydroxide, magnesium hydroxide, magnesiumtrisilicate, simethicone™ and magaldrate the % availability of fexofenadine decreased (Table 1).

The *in vitro* availability of fexofenadine with antacids in buffer of pH 7.4 was performed by the same procedure in which % availability of fexofenadine was 0.198%, respectively. When antacids were added to fexofenadine, % availability with calcium hydroxide was same 0.198% but with sodium carbonate, calcium carbonate, aluminum hydroxide, magnesium carbonate, magnesium hydroxide, magnesiumtrisilicate, simethicone™ and magaldrate the % availability of fexofenadine increased as shown in Table 2.

The *in vitro* availability of fexofenadine with antacids in simulated intestinal juice was performed by the same procedure in which % availability of fexofenadine with magnesium carbonate decreased. The % availability of fexofenadine was 0.072 %. Moreover, this study signifies that with sodium carbonate, calcium carbonate, calcium hydroxide, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate,

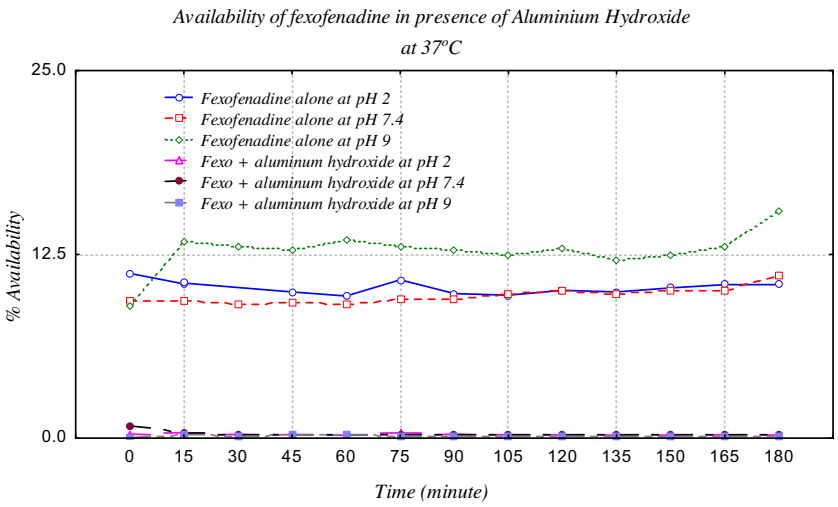


Figure 1 Availability of fexofenadine in presence of aluminum hydroxide at 37 °C.

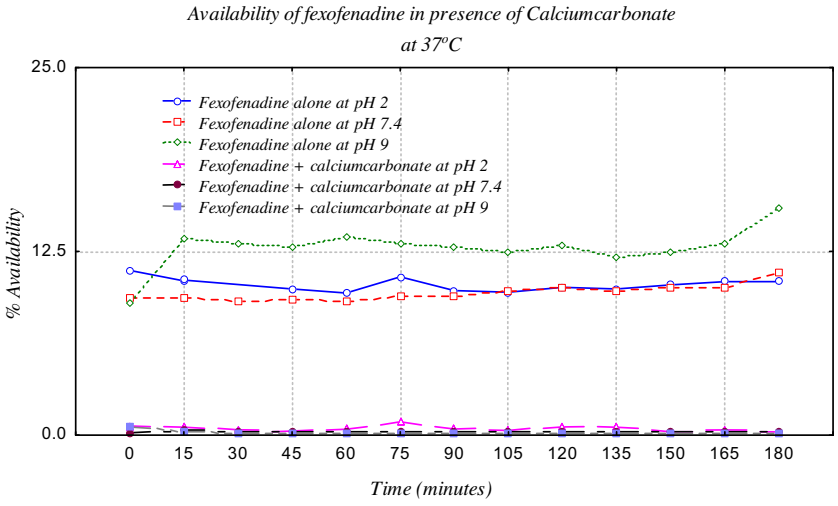


Figure 2 Availability of fexofenadine in presence of calciumcarbonate at 37 °C.

simethicone and magaldrate the % availability of fexofenadine was increased as shown in Table 3.

The *in vitro* availability of fexofenadine was found to be markedly retarded in the presence of few antacids while in most of the cases the drug contents appeared to be more than the drug added which reflects the possible complexation of these di- and tri-valent metal cations with fexofenadine. Moreover, these studies indicated that fexofenadine was powerfully adsorbed on calcium hydroxide, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, simethicone™ and magaldrate in simulated gastric juice, with calcium hydroxide in simulated intestinal juice and there was no adsorption of fexofenadine with calcium hydroxide in buffer of pH 7.4, respectively.

3.3. Fexofenadine antacids interaction by HPLC

10 mL fexofenadine solution and 0.2 g antacid were taken in a conical flask and the flask was shaken for 2 h at 37 °C, afterward the aliquots were filtered through a 0.45 μm Millipore™ filter paper. The mobile phase was prepared by mixing methanol and 6.8 g monobasic potassium phosphate in 1000-ml water and pH was adjusted to 7.4 with potassium hydroxide. The composition was methanol: phosphate buffer, 35:65 (v/v), respectively. The injection volume was 10 μL and the run time was 5.0 min. The mobile phase was filtered using a 0.45-μm membrane filter (Millipore) and degassed in ultrasonic bath. The mobile phase flow rate was 1.0 ml min^{-1}. Samples were injected through a 20 μL loop at ambient and the retention time for fexofenadine was 3.65–3.75 min (Arayne et al., 2009). Peak area and percentage of fexofenadine recovered have been discussed in Table 4. Peak areas were in contrast with standard fexofenadine solutions to evaluate the degree of interaction of fexofenadine with antacids. The chromatograms of adsorption studies carried out at HPLC have been shown in Figs. 7 and 8. In simulated gastric juice the percentage recovery of the fexofenadine increased in case of sodium bicarbonate (110.3%), magnesium carbonate (121.7%) and

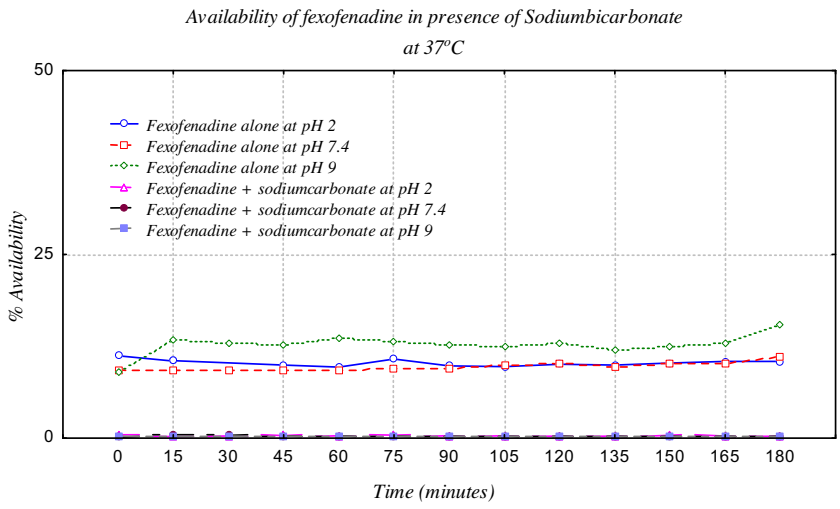


Figure 3 Availability of fexofenadine in presence of sodiumbicarbonate at 37 °C.

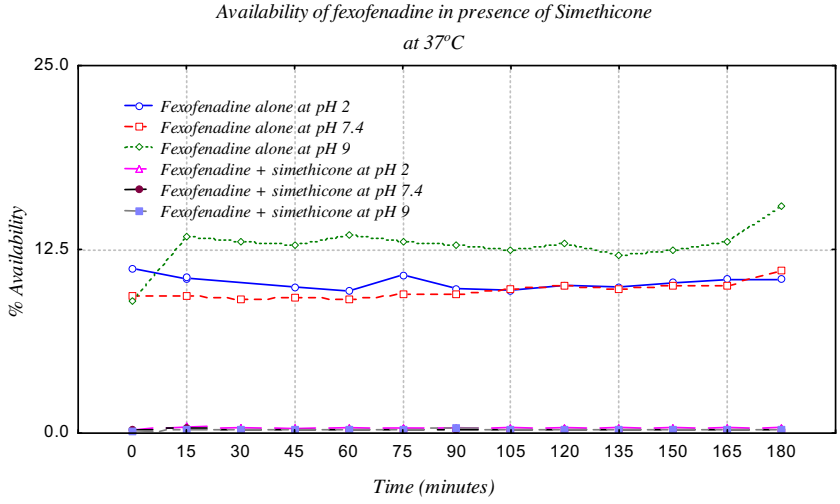


Figure 4 Availability of fexofenadine in presence of simethicone at 37 °C.

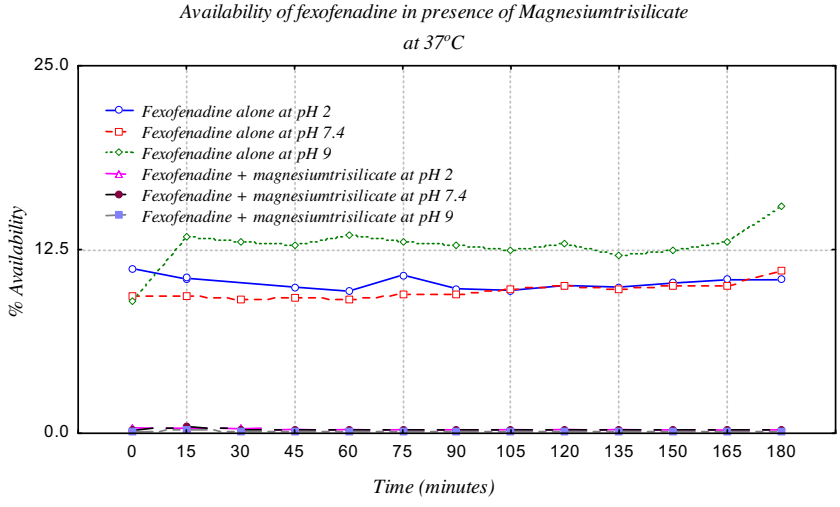


Figure 5 Availability of fexofenadine in presence of magnesiumtrisilicate at 37 °C.

Table 4 Adsorption studies (%) of antacids with fexofenadine analyzed by reversed-phase HPLC.

S. no	Sample	Simulated gastric juice		Simulated intestinal juice	
		Peak area	% Recovery	Peak area	% Recovery
1	Fexofenadine	20761	100.0	19236	100
2	FX + Sodium bicarbonate	22909.4	110.3	25103.8	115.03
3	FX + Megaldrate	13068.2	69.5	22952.4	109.29
4	FX + Calcium carbonate	32498.1	107	26865.9	110
5	FX + Magnesium carbonate	16595.6	121.7	8050.77	43.65
6	FX + Aluminum hydroxide	11683	68.5	20783.6	115
7	FX + Magnesium hydroxide	27856.6	91.9	21482.9	104
8	FX + Magnesium tri silicate	12301.5	54.4	19207.5	110.38
9	FX + Simethicone	30101.7	89.4	18535.3	122
10	FX + Calcium hydroxide	11610.3	50.0	20266.9	106.01

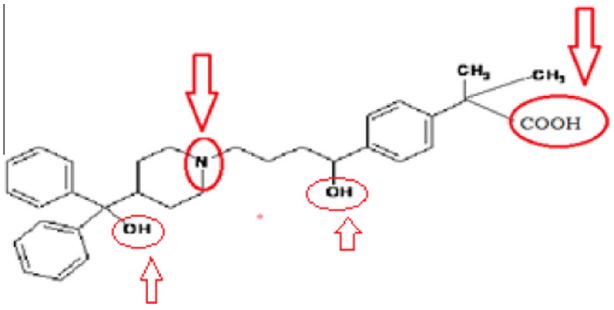
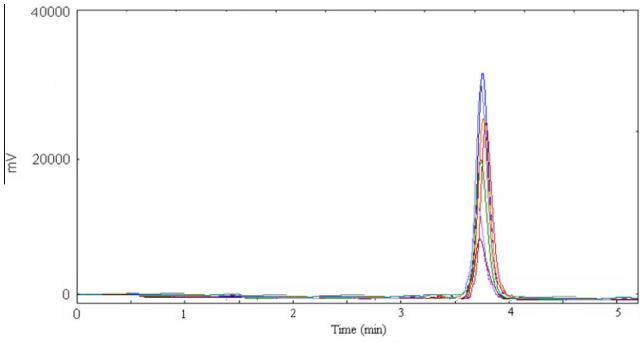
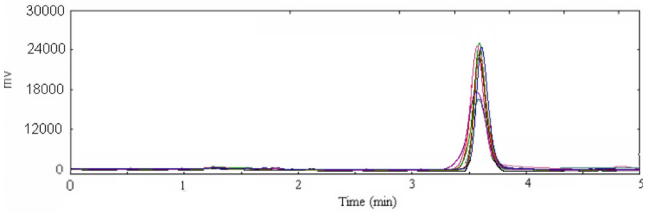


Figure 6 Possible binding sites at fexofenadine.



Fexofenadine-antacid adsorption studies in simulated gastric juice by HPLC

Figure 7 Fexofenadine–antacid adsorption studies in simulated gastric juice by HPLC.



Fexofenadine-antacid adsorption studies in simulated intestinal juice by HPLC

Figure 8 Fexofenadine–antacid adsorption studies in simulated intestinal juice by HPLC.

in all other antacids it decreased while in simulated intestinal juice the percent recovery of fexofenadine increased in case of sodium bicarbonate (115.03%), megaldrate (109.29%), Magnesium trisilicate (110.38%) and calcium hydroxide (106.01%). Fexofenadine (Fig. 6) has piperidine nitrogen and at tertiary carbon it has a carboxylic group and that is why it subsists as a zwitter ion in aqueous media at physiological pH. These two possible sites are responsible for complex formation and fexofenadine–antacid interaction takes place.

4. Conclusion

The fexofenadine antacid interaction has been carried out on both UV spectrophotometer and HPLC and the results reveal that the percentage availability of fexofenadine has been wide-ranging in case of various antacids and the piperidine ring, a carboxylic group and two hydroxyl groups illustrate that it has a significant affinity to form charge transfer complexes.

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